



Attorney Ref. No. 51588 62015

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Redmond et al. Confirmation No. 9723
U.S. Serial No. 09/781,577 Examiner: Barrett, Thomas
Filed: February 12, 2001 Group Art Unit: 3738
For: PHOTOCHEMICAL TISSUE BONDING

EXPRESS MAILING CERTIFICATE

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, Label No. _____, addressed to MS Amendment Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: June 15, 2005Signature: Danise Kacinski
Danise Kacinski

DECLARATION OF MICHAEL R. HAMBLIN, PH.D.

1. I, Michael R. Hamblin, Ph.D., do hereby declare that I am an Associate Professor of Dermatology, Wellman Laboratories of Photomedicine, Harvard Medical School and am familiar with the technology described in United States Patent Application Serial Number 09/781,577 (the '577 application). My experience and professional background are summarized in the curriculum vitae previously submitted on April 2, 2004.
2. This Declaration is intended to supplement and clarify my Declaration signed on April 2, 2004 in which I reviewed United States Patent No. 5,552,452 ("the Khadem patent") cited by the Examiner in the December 2, 2003 Office Action in reference to the '577 Application.
3. I have again reviewed the Khadem patent and maintain my previous conclusion that the Khadem patent fails to enable a practitioner to effectively use a photosensitizer in tissue bonding without the use of an exogenous substrate. At the time that the '577 application was filed, the Khadem patent would not have provided one of ordinary skill

in the art with the ability to combine its teachings with his own knowledge, in order to conduct tissue bonding in the absence of an exogenous substrate.

4. I have reviewed the Office Action dated July 19, 2004 and the Advisory Action dated March 14, 2005. The Examiner of the '577 application has taken the position that the following description at column 7, lines 18-31 of the Khadem patent provides explicit guidance for bonding tissue with a photosensitizer and "peptides or proteins located naturally within the tissue area."

The present invention also encompasses methods for tissue closing or wound healing wherein the actual preparation of a separate protein or peptide containing composition is not necessary. Such methods utilize the peptides or proteins located naturally within the tissue area as in situ protein containing compositions. To form an adhesive connection between biological tissues in this manner one would form a biologically effective amount of a tissue adhesive combination at the tissues by applying only the photosensitizer component to the tissues. One would then again apply electromagnetic radiation (to) the tissue adhesive combination thus formed in a manner effective to promote the formation of an adhesive connection between the tissues.

5. I respectfully disagree with the Examiner's conclusion. This paragraph, as well as the remaining disclosure in the Khadem patent, is lacking in sufficient detail to enable a practitioner to conduct such methods without an exogenous substrate. As I have previously stated, there is no description of specific tissues in which the methods at column 7 lines 18-30 can be effectively practiced, no indication of specific photosensitizers (or excitation wavelengths thereof) that will be effective in the absence of the substrate and perhaps most telling, no exemplification of methods for creating a tissue seal in the absence of the substrate. This paragraph merely *proposes* a method that would not require an exogenous substrate, however, its description is so lacking in both detail and clarity that it cannot be followed by a practitioner without undue experimentation.

6. As a specific example of the lack of guidance in the Khadem patent, Table 1 is clearly flawed as to the use of Rose Bengal. In Table 1, the Khadem patent teaches excitation of Rose Bengal at 600-670 nm. However, Rose Bengal is not active within

this wavelength range (See Figure 1, Lambert et al., (1999) J. Phys. Chem. B, Vol. 103 No. 18, attached under Tab 1).

7. I have recently been provided with a copy of the Declaration submitted by inventor John Khadem, M.D. during the prosecution of the Khadem patent. The Khadem Declaration is attached under Tab 2. Dr. Khadem conducted experiments to demonstrate that photosensitizer formulations used according to his invention must contain at least 1% exogenous protein substrate in order to effectively bond tissue. Dr. Khadem administered four different photosensitizer and protein formulations, having either 18% fibrinogen, 0.9% fibrinogen, 0.27% alpha crystalline or 0.27% beta crystalline, to human cadaver eyes containing an incision. An Argon laser was applied to the incision for two minutes and mean bursting pressures were recorded. Dr. Khadem concluded that formulations comprising less than 1% protein completely failed to provide any adhesive properties.

8. As one skilled in the art of photochemical tissue bonding, at the time that the Khadem Declaration was filed, I would have concluded from the results in the Khadem Declaration that tissue bonding could not effectively occur unless application of the photosensitizer was accompanied by at least 1% exogenous protein substrate and therefore, that formulations having less than this amount of exogenous substrate (including no exogenous substrate whatsoever) could not be effective.

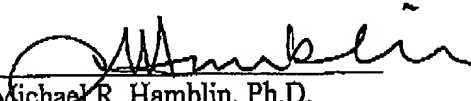
9. It is my understanding that the Advisory Action dated March 14, 2005 implies that the methods of column 7 lines 18-30 in the Khadem patent could potentially be effective, so long as the donor tissue provided a "peptide or protein located naturally within the tissue area." However, the donor tissue in the Khadem declaration (human cadaver eyes) would have contained the endogenous protein envisioned by the Khadem patent (e.g., endogenous collagen). As shown by the Khadem Declaration, the presence of such endogenous protein was not sufficient to bond tissue, even when supplemented by 0.9% fibrinogen. Therefore, the Khadem Declaration shows that Dr. Khadem himself was unable to conduct the methods of column 7 lines 18-30, which depend on the use of

an endogenous protein substrate (i.e., "peptides or proteins located naturally within the tissue area").

10. In conclusion, the Khadem patent fails to provide sufficient guidance to one of ordinary skill in the art with respect to methods of producing a tissue seal without administration of an exogenous substrate. Moreover, the teachings in the Khadem patent could not be combined with the general knowledge in the art in order to conduct tissue bonding in the absence of an exogenous substrate, as exogenous substrates were generally believed to be required for such tissue bonding.

11. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated Jun 13, 2005

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